



A review on mouth dissolving tablets

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ABSTRACT

Now a day's oral route of drug delivery considered as most convenient and economical method of drug delivery system. But for pediatric, geriatric, and bedridden patients it is difficult to swallow solid dosage form like tablets and capsules and may feel difficulty to take liquid dosage forms because of hand tremor. An active patient who is busy and traveling and may not access to water it's a problem to administer a drug. By formulating mouth dissolving drug delivery system (MDDDS) all these drawbacks can be overcome. It has the advantage that it can avoid fast pass metabolism too. Mouth dissolving tablets are designed to be dissolved on the tongue rather than swallowed whole. So it will release the drug as soon as it will come in contact with saliva. This review article focused on various techniques involved in manufacturing of mouth dissolving tablets (MDTs) ranged from patented to non patented technologies. Characteristics of MDTs, advantages, disadvantages, factors responsible for sublingual absorption, challenges in formulating mouth dissolving tablets are discussed. This article demonstrate various evaluation tests of mouth dissolving tablets like weight variation, crushing strength, measurement of tablet porosity, friability, wetting time, *in-vitro* drug release, disintegrating test, modified disintegration test, water absorption ratio and stability studies.

Keywords: Mouth dissolving drug delivery system, MDTs, fast pass metabolism.

INTRODUCTION

Oral drug delivery is the preferable route for drug administration among all the routes used for drug delivery. Various types of dosage forms are manufactured for administration of drug via oral route. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly the patient compliance. Tablets and capsules are most popular dosage forms administered orally. But these dosage forms have some

disadvantages like for patients who feel difficulty in swallowing. Dysphagia is a medical condition in which symptoms like difficulty or discomfort in swallowing^{1,2} experienced. It is common among all age group and more specific with geriatric and pediatric population along with institutionalized patients and patients with nausea⁴. To improve treatment compliances of such patients mouth dissolving tablet or orally disintegrating tablet is a better alternative for oral medication because these tablets solves this problem as it does not mean to be swallowed⁷. These tablets dissolve in mouth when

come in contact with saliva. It is estimated that 50% of the population is affected by this problem, which results in high incidence of noncompliance and ineffective therapy³. They may exert its action locally or have systemic action. ODTs showed that although disintegration time ranged from a few seconds to longer than a minute, a large majority of these products have in-vitro disintegration time of approximately 30 seconds or less⁵. ODTs can be interchangeably used for terms like orally disintegrating, orodispersing, mouth-dissolving, rapid disintegrating tablets, fast-dissolving multiparticulate, fast-melting, fast dissolving freeze dried wafers, quick-dissolve and porous tablets⁶.

In some particular instances mouth dissolving tablets (MDTs) may provide improved safety and efficacy. Use of mouth dissolving tablets have some limitations like patients who have Sjögren's syndrome or dryness of the mouth due to decreased saliva production or take anticholinergic medications may not suitable to take MDTs⁶.

MOUTH DISSOLVING TABLETS SHOULD HAVE FOLLOWING CHARACTERISTICS^{8,9}

- Should dissolve and disintegrate in the mouth within a few seconds
- Require no water for oral administration
- Should give pleasant mouth feel after administration of the tablet
- After oral administration they should leave minimal or no residue in mouth
- Exhibit low sensitivity to environmental conditions such as temperature and humidity
- Can be manufactured by using conventional equipments at low cost

ADVANTAGES OF MOUTH DISSOLVING TABLETS^{10,11}

Due to the following advantages mouth dissolving tablets considered as a novel drug delivery system:

- Rapid absorption and high bioavailability associated with almost immediate onset of pharmacological action.
- Suitable for patients, who feel difficulties in swallowing such as geriatric, paediatric and psychiatric patients.
- First pass metabolism and decomposition from gastric acid can be avoided.

- These have good stability compare to liquid dosage forms mean while shows high bioavailability almost equal to that of liquid dosage form.
- The risk of choking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.

DISADVANTAGES OF MOUTH DISSOLVING TABLETS^{12,13}

MDTs have following drawbacks:

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
- Mouth dissolving tablets need special packing for properly stabilization and safety of stable product.

FACTORS RESPONSIBLE FOR SUBLINGUAL ABSORPTION¹⁴

Lipophilicity of drug:

For effective sublingual drug absorption the drug must have slightly higher lipid solubility for passive absorption.

p^H and pK_a of saliva:

The p^H of saliva is 6.0. For better absorption drug should remain unionized at this p^H.

Solubility in salivary secretion:

The drug should be soluble in aqueous buccal fluids.

Binding to oral mucosa:

Binding between drug and oral mucosa should be poor.

Thickness of oral mucosa:

The thickness of oral mucosa is 100-200 micrometer which is less as compared to buccal thickness (500-800 micrometer).

Partition co-efficient:

The drugs which have oil to water partition co-efficient within the value of 40-2000 are suitable for absorption through sublingually.

CHALLENGES IN FORMULATING MOUTH DISSOLVING TABLETS¹⁵

Palatability

As the name indicates mouth dissolving tablet is meant to be disintegrate or dissolve in patient's oral cavity there by release the active entity which come in contact with the taste buds; hence it is needed to mask bitter taste of the drug.

Mechanical strength

Mouth dissolving tablets are made to disintegrate in few seconds, so they are prepared with low compression force. This makes the tablet friable, difficult to handle and require specialized peel-off blister packing which increases the cost of production.

Hygroscopicity

Several mouth dissolving tablets are hygroscopic in nature and unstable at normal conditions of temperature and humidity. So, these tablets require specialized packaging.

Aqueous solubility

Water soluble drugs form eutectic mixtures, which results in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process.

CHARACTERISTICS OF A DRUG TO BE FORMULATED AS MDTs^{15, 16}

Followings are some conditions should be considered before choosing a drug candidate for MDT:

Drugs candidates suitable for manufacture as mouth dissolving tablets:

- Good stability in water and saliva.
- Drug which undergo first pass metabolism and/or produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism.
- Drugs to be formulated as MDTs should have absorption window in the oral cavity and in pre-gastric region.
- Drug that are considered ideal for MDT should capable of diffuse and partition into the epithelium of the upper GIT ($\log P > 1$, or preferable > 2) and able to permeate oral mucosal tissue.

Drug unsuitable for manufacture as mouth dissolving tablets:

- Drug with short half-life and frequent dosing is not a suitable candidate for MDT.
- A very bitter tasting drug or drug having unacceptable taste is a bad candidate to be formulated as MDT.

- Patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for MDT formulations.
- Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.

TECHNOLOGIES FOR PREPARATION OF MOUTH DISSOLVING TABLETS

Various technologies used for preparation of mouth dissolving tablets. They are broadly categories as follows:

Non-patented technologies

Melt granulation, direct compression, freeze drying or lyophilization, sublimation, mass extrusion, spray drying etc. are non-patented methods used for preparation of mouth dissolving tablets.

Patented technologies

From various patented technologies used for manufacturing of mouth dissolving tablets some are: Zydis technology, DuraSolv technology, OraSolv technology, Flash dose technology, Flashtab technology, WOWTAB technology.

NON-PATENTED TECHNOLOGIES

Melt-granulation

Melt granulation process utilizes materials that are effective as granulating fluids when they are in molten state. Then agglomerated powders are cooled which solidifies the molten materials. Both processes i.e. molten agglomeration and cooling solidification were accomplished in a high shear collette gral mixer equipped with a jacketed bowl. In this method there is granulating solvent need not be used as conventional wet granulation process¹⁷.

Direct compression

As the name indicates it is the process in which tablets are compressed directly from powder material without modifying the physical nature of materials itself. It is the most easiest method for tablet compression. Directly compressible tablets must possess good flow property. As it involves fewest processing steps, conventional equipment and low manufacturing cost makes it preferable method for tablet compression. Disintegration and solubilization of directly compressible tablets can be

modified by using proper concentration of suitable disintegrants, water soluble excipients and effervescent agents.

Freeze drying or Lyophilization

This technique involves drying of pharmaceutical product by technique of sublimation. In this process water passes directly from solid state (ice) to vapor state without passing through liquid phase. The materials to be dried is first frozen and then subjected under a high vacuum to heat so that frozen liquid sublimates leaving only the solid, dried components of the original liquid²³. This method is useful for heat sensitive materials or materials which readily react with oxygen. Lyophilization results in preparation which is highly porous, with a very high specific surface area, which dissolves rapidly and show improved absorption and bioavailability²⁴.

Sublimation^{18, 19, 20,}

Even though a tablet contains highly water soluble ingredients, its low porosity reduces water penetration into the matrix which leads to slow dissolution. Tablets with high porosity are formed by compressing tablet ingredients along with volatile substances. After compression tablets are kept in oven for complete removal of volatile substances. Substances like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor hexamethylene tetramine, naphthalene, phthalic anhydride, urea, urethane etc are used as sublimating agents.

Mass extrusion^{21, 22}

In this technology softened active (tablet mixture) blend expelled through extruder or syringe to get cylinder shaped extrude. To soften active blend solvent mixture like water soluble polymer and methanol are used. These extrudes are cut into even segments using heated blade to form tablets. This technology is also useful to coat granules thereby mask bitter taste of active component.

Spray drying

Highly porous, fine powders can be produced by spray drying process. The formulations that were produced contain hydrolyzed and unhydrolyzed gelatin as supporting agent, mannitol as bulking agent, sodium starch glycolate/cross carmellose sodium as

disintegrants and an acidic material (e.g. citric acid) and/or alkali material (e.g. sodium bicarbonate) to enhance disintegration. Tablets made from spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium²⁵.

PATENTED TECHNOLOGIES

Zydis technology^{26, 27}

Zydis, is a excellent technology for manufacture of fast dissolving or disintegrating tablets. When tablets made by this process placed on the tongue, dissolve in less than 3 seconds. Zydis tablet is made by lyophilization or freeze drying technique is highly porous in nature. The drug is physically trapped in a water soluble matrix usually consisting of gelatin.

A major claim of Zydis product is increased bioavailability compared to conventional tablets as it predominately absorbs buccal, pharyngeal and gastric regions which avoids hepatic first pass metabolism.

These tablets are very lightweight and fragile in nature so must be dispensed in a special blister pack. Patients are advised to peel the back film to release the tablet. Zydis formulations have poor stability at higher temperature and humidity.

DuraSolv technology²⁸

DuraSolv is a patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. DuraSolv is an appropriate technology for products requiring low amount of active ingredients.

OraSolv technology²⁸

OraSolv is CIMA Lab's technology used to develop oral disintegrating dosage form. When the tablet disintegrates, the drug microparticles are released and swallowed as a slurry or suspension. If the drug microparticles are not taste-masked, some dissolution may occur in the mouth. Upon swallowing, the microparticles reach the patient's GI tract, where complete dissolution and systemic absorption of the drug takes place. If the drug particles are taste masked, dissolution occurs in the GI tract.

The OraSolv ODT technology uses taste-masked drug microparticulates in a formulation that enhances tablet

disintegration. Carbon dioxide is generated by a reaction of the formulation components upon exposure to water (saliva in the mouth). This causes a sensation in the mouth that is pleasant to the patient and tends to stimulate further saliva production, which also aids in disintegration.

WOWTAB technology²⁹

WOWTAB technology employs a combination of low and high moldability saccharides to produce fast dissolving tablets using conventional granulation and tableting techniques. A saccharide having low moldability was granulated with a saccharide having high moldability as a binder. The low-moldability saccharides were used as the main component. The tablets show as adequate hardness and fast disintegration and dissolution when put in the mouth.

Flash dose technology²⁹

Flash dose technology has been patented by Fuisz. Nurofenmeltlet, a new form of Ibuprofen as melt-in-mouth tablets, prepared using flash dose technology is the first commercial product launched by Biovail Corporation. A flash dose tablet consists of self binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing.

Flashtab technology³⁰

Flashtab technology produces tablets by compression of granular excipients. This technology uses almost the same excipients as do conventional compressed tablets. Excipients used in this technology comprise two groups of components: disintegrating agents, such as carboxy methyl cellulose or insoluble reticulated poly vinyl pyrrolidone; and swelling agents, such as carboxy methyl cellulose, starch, modified starch, carboxy methylated starch, microcrystalline cellulose and possibly directly compressible sugars. The mixture of excipients is prepared by either dry or wet granulation methods. The produced tablets are known to have satisfactory physical resistance and disintegrate in the mouth within 1 minute.

EVALUATION OF MOUTH DISSOLVING TABLETS

Evaluation of mouth dissolving tablets is to be assessed according to Pharmacopoeias. They are as follows:-

Weight variation

Uniformity of tablets can be demonstrated by weight variation or content uniformity³¹. 20 tablets should be weighed individually and average weight is calculated. Individual tablet weight should compare with average tablet weight. According to USP, more than two tablets should not fall outside the percentage limit and no tablet must not differ by more than 2 times the percentage limit.

Crushing strength

The force required to break a tablet by compression in the radial direction is known as crushing strength. It is an important parameter in the formulation of mouth dissolving tablets because excessive crushing strength significantly reduces the disintegration time³².

Measurement of tablet porosity^{33, 34}

A definite range of porosity is essential for tablet preparation as it affects mechanical strength and intrusion of water into the tablet. The porosity of each tablet can be determined using the following equation:

$$\text{Porosity} = \frac{\text{Volume of tablet} - \frac{\text{Weight of tablet}}{\text{True density of ingredients}}}{\text{Volume of tablets}} \times 100$$

Friability

Friability test of tablets should be done to ensure the tablets are stable to abrasion or not. Friability is tested using Roche friabilator. 20 tablets are weighed and placed in the plastic drum attached to the machine rotated at 25 rpm for 100 revolutions. Then tablets are cleaned with a cloth and weighed again. Percentage friability is calculated as follows:

$$\% \text{ Friability} = (W_0 - W) / W_0 * 100$$

Where, W_0 = Initial weight of 20 tablets

W = Weight after 100 revolutions

The weight loss should not be more than 1% w/w.

Wetting time and water absorption ratio

Wetting time^{35, 36, 37}: Wetting time describes the time taken for the tablet to disintegrate when placed motionless on the tongue.

The inner structure of tablets and hydrophilicity of excipients used in tablet formulation affects time required to wet the tablet. To describe water penetration rate to the powder bed, Washburn E.W. (1921) proposed the following equation

$$dl/dt = r\gamma\cos\theta/(4\eta l)$$

where, l is the length of penetration, r is the capillary radius, γ is the surface tension, η is the liquid viscosity, t is the time and θ is the contact angle. A linear relationship exists between wetting time and disintegration time of the tablets. Thus wetting is first step for a tablet to disintegrate.

A piece of tissue paper folded double was placed in a petri plate of internal diameter is 6.5 cm containing 6 ml of water. The tablet should place on the paper and the time for complete wetting of the tablet was measured in seconds and noted as wetting time. The method was slightly modified by maintaining water at 37°C ³⁸. The wetted tablet was then weighed and the water absorption ratio, R , was determined according to the following equation³⁹:

$$R = 100 (W_0 - W_f)/W_f$$

Where, W_0 is weight of the tablet before water absorption and

W_f is weight of the tablet after water absorption

Moisture uptake studies⁴⁰

As mouth dissolving tablets are made up of hydrophilic excipients there have a chance that they may absorb increased amount of moisture which greatly affects stability of moisture sensitive products. To study moisture uptake by tablets, ten tablets are kept in a desiccator (containing calcium chloride) for 24 hrs at 37°C for drying. After weighing the tablets are stored in 75% RH for 2 weeks. Saturated solution of sodium chloride was kept at bottom of the desiccators for three days to maintain this humidity. On the tenth day tablets were re-weighed and the percentage increase in tablet weigh was recorded.

Disintegration test

The *in-vitro* disintegration time was determined using disintegration test apparatus specified in IP 1996. Distilled water may be taken as media and temperature is maintained at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$. Six tablets were placed in six tubes of the apparatus one tablet in each tube and disc was added to the tubes. Time taken to complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured as disintegration time.

Mordified disintegration test⁴¹

Due to several limitations of standard disintegration procedure it is adequate to measure very short disintegration time. A petridish (10cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of the petridish and the time for the tablet to completely disintegrate into fine particles was noted.

In-vivo disintegration time⁴²

In-vivo disintegration time is determined by placing the tablet in the mouth of healthy human volunteers.

Dissolution test⁴¹

The dissolution rate of the drug from the primary particles of the tablets is the important factor in drug absorption and for many formulations is the rate – limiting step. Therefore, a dissolution time is more indicative of the availability of a drug from a tablet than the disintegration test. Dissolution test for mouth dissolving tablets is same as that of conventional tablets. Test must be carried out as prescribed in the monograph. Medias such as 0.1N HCl and buffers (p^{H} 4.5 to 6.8) may be used for the evaluation.

Stability study

Stability study of mouth dissolving tablets is done according to ICH guidelines for accelerated studies after suitable packaging at following conditions:

- 1) $40 \pm 1^{\circ}\text{C}$
- 2) $50 \pm 1^{\circ}\text{C}$
- 3) $37 \pm 1^{\circ}\text{C}$ and RH $75\% \pm 5\%$

Tablets are withdrawn at specified time period and analysed for various parameters like visual defects, hardness, friability, disintegration, dissolution etc.

CONCLUSION

MDTs found to be brilliant drug delivery system for geriatric, pediatric, bedridden, psychotic patients and for those patients who are busy in travelling, has difficulty in swallowing and may not have access to water. This article discussed about recent advances adopted for manufacturing of MDTs. Rapid onset off action, quick absorption, improved bioavailability & efficacy, avoid fast pass metabolism and better patient compliance made MDTs to attract attention in the research and industrial fields.

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